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Dysfunction of stress responsive systems as a risk factor for functional somatic syndromes

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Abstract

The etiology of functional somatic syndromes or disorders (FSDs) is generally considered to be a multifactorial interplay between psychological, biological, and social factors. One of the most investigated biological factors is stress responsive system dysfunction. Despite more than twenty years of research of the autonomic nervous system and the hypothalamic-pituitary-adrenal axis, however, it is yet unknown whether dysfunctions in these systems play a causal role in the etiology of FSDs and whether they

are generic or FSD-specific. In this review, we will give an overview of available evidence on whether or not alterations in these stress responsive systems can be considered causal risk factors of FSDs. We conclude that although not necessary factors for FSDs in general, lowered cardiac vagal activity and hypocortisolism may be pivotal in the etiology and treatment strategy in subgroups of subjects with a FSD. Such subgroups need to be better identified.

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Keywords: Autonomic nervous system; Functional somatic symptoms; Hypothalamus-pituitary-adrenal axis; Somatoform; Stress; Functional somatic syndromes

Introduction

Psychosocial stress is widely believed to be involved in the development of functional somatic syndromes or disorders (FSDs), such as chronic fatigue syndrome (CFS), fibromyalgia (FM), and irritable bowel syndrome (IBS) [1–3]. The autonomic nervous system (ANS) and hypothalamic-pituitary-adrenal axis (HPA axis) both serve as bodily stress responsive systems [4–6], and psychosocial stress may have the potential to induce chronic under- or overactivity of these stress responsive systems [7–9]. However, alterations in stress responsive systems may not only be a result of psychosocial stress, but may also be a consequence of factors such as concurrent stress, smoking, obesity, medication use, comorbid depressive disorder, or physical inactivity [10,11].

A reason to investigate a potential etiological link between dysfunction of stress responsive systems and FSDs emerges from the idea that dysfunction of the ANS and HPA axis may contribute to increased symptom experience [12–14]. The question remains whether dysfunction of stress responsive systems is actually present in FSDs, whether it is a generic or FSD-specific factor, and whether it could be involved in their etiology or is merely a consequence or epiphenomenon.

In this review, we will systematically assess whether stress responsive system dysfunction satisfies the requirements of being a causal risk factor for FSDs, using a decision tree proposed by Kraemer et al. [15]. In this decision tree, a risk factor is defined as a measurable characterization of each subject in a specified population that precedes the outcome of interest. A characterization that satisfies all requirements for a risk factor except for precedence is a correlate of the outcome. This is crucial, because consequences of outcomes are likely more highly correlated with the outcomes than are risk factors. A risk factor that can change spontaneously within a subject or that can be changed with an intervention is a variable risk factor. The term causal risk factor can only

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be used when a variable risk factor changes the risk of the outcome when it is manipulated (see Fig. 1). We will apply this decision tree to the available literature on ANS and HPA axis alterations in FSDs and studies on FSD-related clusters of functional somatic symptoms (FSSs).

ANS activity and FSDs

Are alterations in ANS activity correlated with FSDs?

A widely used proxy for ANS function is heart rate variability (HRV), from which a measure of cardiac vagal activity can be derived. A meta-analysis including 14 studies indicated statistically significant lower baseline cardiac vagal activity in subjects with a FSD compared to controls [16], with no apparent differences between CFS, FM, and IBS. This meta-analysis thus suggests that reduced parasympathetic activity possibly causes increased arousal and is a generic correlate of FSDs. However, sensitivity analyses also suggested the presence of publication bias. Moreover, there was unexplained heterogeneity in the effect sizes of studies included in the meta-analysis, possibly related to a variety of methodological shortcomings, including biased selection of control subjects and potential confounding. A population-based study published shortly afterwards, that adjusted for factors such as gender, age, body mass index, medication use, and physical inactivity, found lower cardiac vagal activity in 30 CFS subjects compared to 38 healthy controls, but this difference did not reach statistical significance [17]. A population-based study on FSSs in 774 adults demonstrated that decreased cardiac vagal activity was associated with a higher number of FSSs in young to middle-aged adults. Moreover, as was the case in the meta-analysis, this association with lower cardiac vagal activity was generic in the sense that is was similar for different bodily clusters of FSSs (e.g., in the musculoskeletal cluster resembling FM and the gastrointestinal cluster resembling IBS) [18]. In this population-based study, an unanticipated interaction between age and cardiac vagal activity was also found, in which the association between cardiac vagal activity and FSS turned positive for middle-aged to older adults. Interestingly, these results seem to be in line with previously reported age-associated differences in the association between cardiac vagal activity and depression [19].

From the meta-analysis of ANS activity in rest, it was clear that the large variety in methodological procedures may have contributed to equivocal results. This variety is even larger for studies investigating HRV measurements performed during challenge tests. Strategies used to challenge the ANS include measurements during standing, tilt table testing, deep breathing, isometric exercise, treadmill walking, thermal stimuli, rectal balloon distention, and mental stress. Given the variety of challenge

procedures and the fact that reliability of HRV during challenge tests is generally poorer than when measured at rest [20], it is not surprising that results of studies towards ANS activity during challenge in FSD patients are mixed. In about half of the studies, no significant differences were found between subjects with a FSD and healthy controls, but in those studies that did find significant differences, cardiac vagal activity was always lower or responsiveness was decreased in FM and CFS, and most of the time in IBS [11]. In summary, the available evidence suggests reduced parasympathetic activity to be a generic correlate of FSSs and FSDs.

Do alterations in ANS activity precede FSDs?

As the ANS innervates several organs, certain sensations and misinterpretation of peripheral physiological arousal may result in the experience of FSSs [13,14]. Examples of FSS that may result from misinterpretation of autonomic physiological arousal are functional abdominal pain in case of decreased gastrointestinal peristalsis, and functional musculoskeletal pain in case of increased muscle tension. Although theoretically attractive, it should be noted that studies investigating a relation between changes in ANS activity and experience of symptoms on the short-term are scarce. We are aware of one study that assessed whether alterations in HRV directly precede symptom experience. This study was performed in a nonclinical student population of 18 young females scoring high on a list of hyperventilation-related FSSs and 18 young females scoring low on this list. Although the group high on FSSs reported a significantly larger number of somatic symptoms after mental stress and breathing of CO₂-enriched air compared to the group low on FSSs, there were no accompanying differences in cardiac vagal activity [21]. Therefore, the authors argue that persons scoring high on hyperventilation-related FSSs possibly have an exaggerated perception of normal peripheral physiology. However, this finding in a specific subgroup of FSSs in healthy students should be replicated in larger populations suffering from clinically relevant FSDs.

Longitudinal studies on whether alterations in ANS activity precede FSDs in the long term are lacking. Available evidence is restricted to the previously mentioned population-based study on ANS activity and FSSs, which showed that decreased cardiac vagal activity was associated with FSSs after 2 years of follow-up in younger adults. Instead, increased cardiac vagal activity was associated with FSSs after 2-year follow-up in middle-aged to older adults [18].

Can ANS activity be changed and does change improve FSDs?

Several medications influence ANS activity [22,23]. Furthermore, there is some preliminary evidence that interventions such as HRV biofeedback [24] or

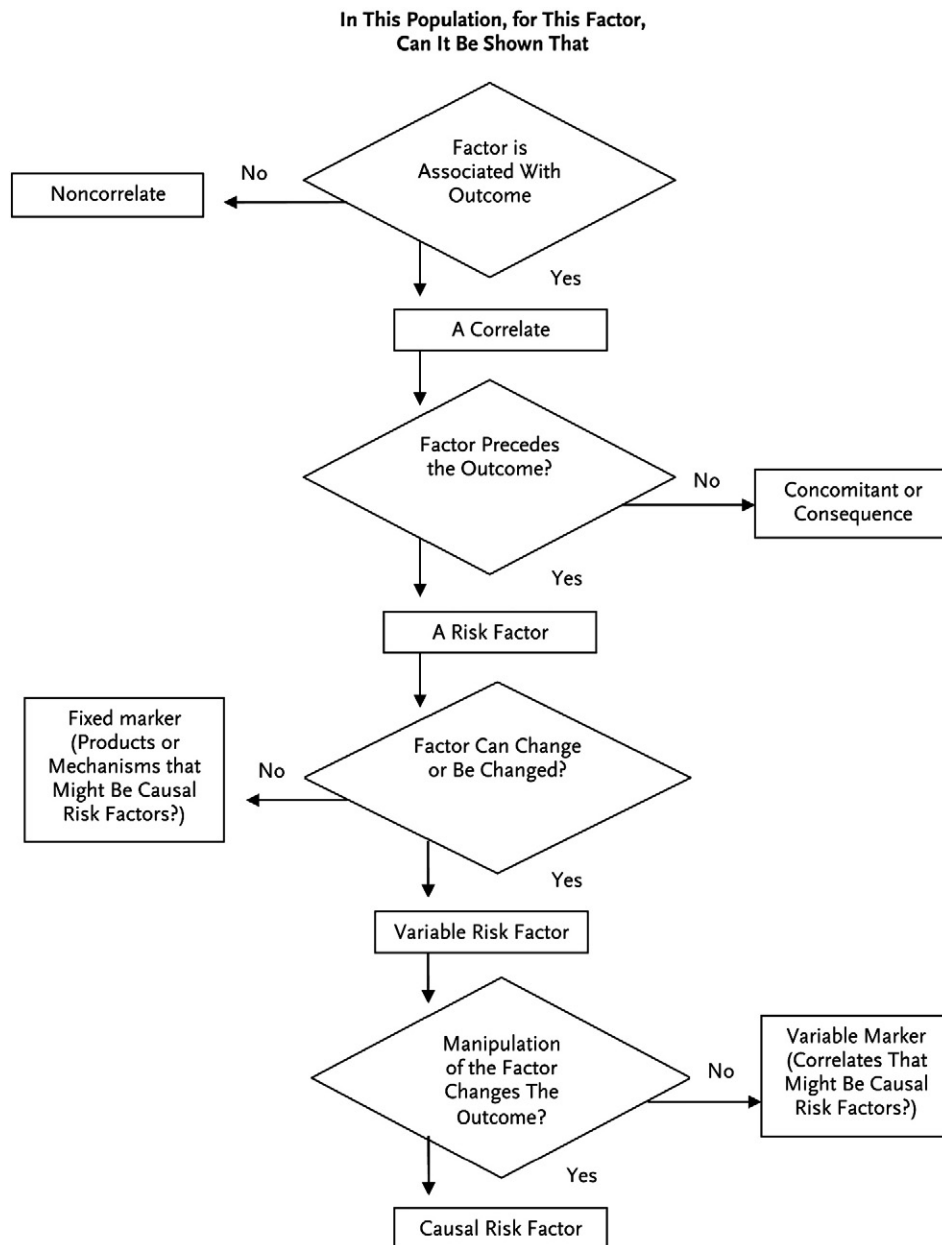


Fig. 1. The process of elucidation of risk factor status for a factor in a population for a particular outcome. Reprinted with permission from *Arch Gen Psychiatry* 1997;54:341.

meditation [25] can improve cardiac vagal activity. Interestingly, the extent to which ANS activity can be changed may differ by gender or age. For example, exercise training resulted in significant increases in cardiac vagal activity, but these effects were considerably larger in younger compared to older subjects [26]. Gender also has a significant role in these exercise-related changes in healthy young adults, as cardiac vagal activity increased after training and decreased after deconditioning in men, whereas no significant changes were apparent in women [27].

To our knowledge, no study has assessed whether cardiac vagal activity can be manipulated to change FSD outcome.

Conclusions on the role of ANS activity in FSDs

A meta-analysis found lowered cardiac vagal activity in subjects with a FSD, with apparently no differences between CFS, FM, and IBS. When studies found differences, they consistently demonstrated lower cardiac vagal activity in patients with a FSD. Given the potential publication bias, the overall poor methodological quality, and the lack of longitudinal studies; however, it seems not possible yet to firmly reject or accept a role of ANS dysfunction in FSDs, or to differentiate its relative importance across the three FSDs. A population-based study suggested that the results of the meta-analysis on FSDs are not solely due to methodological

limitations, as this study also suggested cardiac vagal activity as a generic risk factor for FSSs in younger adults. The observation that lower cardiac vagal activity precedes new-onset FSSs suggests that alterations in this stress responsive system are not just a concomitant or consequence of FSS. The finding of higher cardiac vagal activity in older adults with FSS warrants further research and better insight. Based on current available evidence, it seems premature to decide whether ANS activity is a correlate of FSDs, let alone whether it is a causal risk factor. Overall, evidence suggests reduced parasympathetic activity as a generic factor, but the inconclusive evidence on the role of the ANS in FSDs requires further study.

HPA axis activity and FSDs

Are alterations in the HPA axis correlated with FSDs?

The findings on the association between the HPA axis and FSD are even more heterogeneous than in ANS studies. Not only mild hypocortisolism or normal cortisol levels, but also hypercortisolism, has been reported [11]. A recent meta-analysis of cross-sectional studies demonstrated that hypocortisolism was present in CFS and possibly in FM, but not in IBS [28]. A relevant subgroup might constitute individuals with childhood trauma, as it has recently been found that decreased cortisol responses to awakening are observed only in those individuals with CFS who reported exposure to childhood trauma but not in individuals without such exposure [29].

In agreement with the meta-analysis, an experimental study on 80 healthy young adults observed that those who scored higher on subjective measures such as pain intensity and pain unpleasantness had a flattened cortisol awakening response (i.e., lower cortisol in the morning) [30]. A small study that examined salivary cortisol levels of 14 healthy office workers during four consecutive weeks also showed that low cortisol levels in the morning and high cortisol levels in the evening were associated with poor self-rated health and fatigue [31]. Differences in the association between cortisol and symptom clusters as found in the meta-analysis on FSDs were not found in a population-based study on FSSs in 741 adults. Taking the role of medication and a large range of potential confounders into account, there was no cross-sectional association between 24-h urinary free cortisol (24-h UFC) and the total number of FSSs experienced in the previous year [32]. In addition, 24-h UFC excretion was not associated with the number of FSSs in any of the bodily clusters.

HPA axis activity can also be measured after a challenge test. A problem is the variety of applied challenges, as many different pharmacological and non-pharmacological stressors are used. Blunted responses and enhanced negative feedback are the main findings in studies on HPA axis function after challenge tests [11,33,34]. It is important to

realize that rest and challenge measurements within a person appear poorly interrelated. For example, the cortisol awakening response and cortisol values after a psychosocial stress test are not correlated [35]. This is surprising given the general idea that those alterations may be representatives of the same underlying HPA axis pathology. Thus, measuring cortisol in rest may reveal other underlying mechanisms than measuring cortisol after challenge tests. Even the naturalistic cortisol awakening response and cortisol levels later in the day are not driven by the same factors, as the genetic influence on the cortisol awakening response is distinct from the heritability of daytime cortisol levels [36]. In summary, when alterations in the HPA axis were detected, hypocortisolism and blunted HPA axis responses were consistent correlates of subgroups of FSDs. Since baseline and challenge stress measurements seem to reflect different processes, it is essential that their different meanings are further elucidated to be able to interpret them appropriately in the process of FSDs.

Do alterations in HPA axis activity precede FSD?

Although acute stress is known to produce analgesia, chronic stress may have the opposite effect, a process mediated by corticotrophin-releasing hormone (CRH) [37,38]. Low cortisol concentration may cause widespread pain and fatigue [12,39]. One study has closely examined whether cortisol levels are related to the experience of FSSs in the short term. In a sample of 121 participants middle-aged adults, it was found that morning cortisol levels were not predicted by prior-day levels of fatigue and physical symptoms, whereas low morning cortisol predicted higher levels of fatigue and physical symptoms later that day. Authors concluded that these results are consistent with a role of cortisol in physiological activation and an influence on physical well-being [40].

The question whether alterations in HPA axis activity predict FSDs in the long term has been subject of a number of prospective studies. Studies focusing on fatigue in specific groups at risk found no predictive role of cortisol in the development of post-infectious unexplained fatigue in 71 primary care patients after 3 or 6 months [41], or in postoperative unexplained fatigue in 161 patients undergoing elective surgery after two days, three weeks, or six months [42]. From a study on fatigue in the general population, however, another picture emerges. Among a group of 4299 former or current civil servants, low cortisol at awakening predicted new-onset fatigue at follow-up approximately 30 months later. The association with new-onset fatigue was independent of factors such as age, gender, waist circumference, smoking, alcohol use, medication use, depressive symptoms, time of waking, sleep duration, sleep disturbances, and stress on the day of sample collection. Furthermore, persistent fatigue assessed two years prior to cortisol measurement was not associated with cortisol secretion, suggesting that the direction of the

association is dominantly from lower cortisol leading to fatigue [43]. Long-term longitudinal studies have not been restricted to unexplained fatigue, but have also been performed in other subgroups of FSSs. Among a group of subjects psychosocially at high risk for chronic widespread pain, lower morning and higher evening salivary cortisol levels predicted new onset of chronic widespread pain, a condition related to FM [44]. The 24-h UFC excretion did not predict development of new-onset FSSs in a 2-year follow-up period in our previously mentioned population-based study [32]. It should be noted that fatigue has not been measured in this study.

Overall, a tentative picture emerges suggesting that a flattened diurnal rhythm of cortisol (i.e., lower morning cortisol and higher evening cortisol levels) is related to the experience of FSSs or FSDs. The finding of the importance of morning cortisol in somatization may not be surprising, because timely cortisol secretion for mobilization of energy resources is necessary to meet upcoming demands of the day [45]. Recent reviews are beginning to elucidate the meaning and relevance of the different aspects of the diurnal rhythm of the HPA axis [46,47].

Can HPA axis activity be changed and does change improve FSDs?

Several medications with the capacity to influence cortisol levels via different pathways are documented [48,49]. Some of these medications may not only confound the association between cortisol and FSDs, but may also be used to change cortisol levels intentionally as an intervention. Psychological interventions also seem able to influence HPA axis activity [50].

It has been tested whether treatment with hydrocortisone improves the symptoms or disability caused by FSDs. Randomized controlled trials have shown that low-dose cortisol replacement therapy lead to short-term reductions in fatigue in CFS [51,52]. Although pharmacologically raising levels of cortisol can temporarily alleviate symptoms, it is not recommended as treatment of choice in CFS. Reasons for caution are a rapid loss of efficacy upon discontinuation, the observation that only a minority of patients gain benefit, and that no pre-treatment factors that predict response to hydrocortisone are identified [33]. Whether the same applies to FM and IBS is unknown. In FM, only one small study in 20 patients, performed over 20 years ago, showed that 10 mg of prednisone daily was not effective over 20 years ago [53]. In IBS, treatment with corticosteroids has never been tested in a trial [54].

The effect of psychological and behavioral interventions on the HPA axis has also been tested in FSDs. Two studies in CFS and FM observed that cognitive behavioral treatment alone or in combination with exercise therapy resulted in restoration of cortisol levels [55,56]. It should be noted that neither study included a control group. Moreover, although these two studies indicated that hypocortisolism in FSDs is

reversible by treatment, they did not specifically examine whether these alterations were due to reducing adverse behavioral consequences, such as sleep disturbances, physical inactivity, or pain experience. Cortisol levels may also have a prognostic value, since it has been demonstrated that lower daily cortisol output and a flattened diurnal rhythm predict a poor response to cognitive behavioral therapy in CFS [57]. Interestingly, it has also been reported that CFS patients who respond less well to cognitive behavioral therapy are the ones who are more persistently physically inactive [58]. However, the question whether non-responders with hypocortisolism in this study might represent a physically inactive group has not been assessed and remains to be answered. Preliminary evidence for physical inactivity as a cause of hypocortisolism rather than a confounder comes from a small study performed in 18 regularly exercising healthy adults. Subjects were asked to discontinue their regular aerobics lessons for one week. The subset of healthy subjects that developed symptoms of pain and fatigue after exercise deprivation was characterized by lower cortisol levels at baseline [59]. Authors of this study speculated that the subset of healthy individuals with lower cortisol levels unknowingly exercise regularly to augment the function of HPA axis and thus suppress symptoms.

Conclusions on the role of HPA axis dysfunction in FSDs

The HPA axis is the most extensively investigated stress responsive system in FSDs. A meta-analysis on this subject found lower cortisol levels in CFS and, possibly in FM, but not in IBS. Although HPA axis alterations are not always found, when studies find differences, lower morning cortisol levels in combination with a flattened diurnal rhythm seems consistent with HPA axis alterations in functional fatigue and musculoskeletal pain. Longitudinal studies suggest that hypocortisolism is a specific risk factor for fatigue and musculoskeletal FSSs. Whether hypocortisolism also has a role in symptom maintenance has not been specifically studied. Based on current available evidence, hypocortisolism is at least a risk factor in subgroups of FSDs. The question whether it also is a causal risk factor remains to be answered.

Future directions for research on dysfunction of stress responsive systems in FSDs

In summary, although hypocortisolism and decreased cardiac vagal activity seem correlates of FSDs, several studies have reported null-findings. An important issue is that individual studies are often underpowered. As an example, the reported effect size of $d=0.32$ in the meta-analysis on cardiac vagal activity in FSDs implicates that in a case-control study, a sample size of 155 in each group is required for 80% power. However, the average sample size of included primary studies was 24 cases (range 8–70), and 20 controls (range 8–38). Several other reasons have been

suggested to explain inconsistencies in available evidence, such as heterogeneity in the patient groups, the lack of epidemiologically comparable control groups, and failure to appropriately adjust for relevant confounders [10,16].

To successfully proceed in this complex field, future research faces the challenge of devising studies that include a theoretical perspective as to why alterations in stress responsive system function might influence the experience of somatic symptoms. Whereas this review has focused on peripheral (i.e., efferent) mechanisms, it is important to realize that this peripheral input is modulated by central (i.e., afferent) mechanisms [60]. Disturbances in function of central nervous system structures are increasingly considered pivotal in the etiology of somatization [61–63]. For example, alterations in activity of the anterior cingulate cortex, a structure that is interconnected with both the ANS and HPA axis, have been associated with pain experience and somatization [60,62]. However, as findings are divergent, the need to establish subgroups in this research area arises [64]. In addition, carefully choosing the optimal methodological strategy is essential. Future studies could employ methods that appropriately account for the time-varying nature of the association by repeatedly assessing activity of stress responsive systems, FSDs, and covariates like body mass index, depression, anxiety, and health behaviors, such as smoking, alcohol use, and physical inactivity, and factors like childhood trauma and other psychosocial stressors [65].

When stress responsive system dysfunction is found to be a causal risk factor for FSDs, its value in clinical or policy applications remains to be evaluated. According to Cohen's conventions, the magnitude of significant associations between stress responsive system function and FSDs is usually small [66]. However, the terms small, medium, and large are relative, not only to each other, but even more particularly to the area of research. With regard to somatization, a plausible cause of small effect sizes is heterogeneity in etiological mechanisms, inherent to many associations studied in psychosomatic research. The fact that an effect size is an average can be important. Whereas a small overall effect size may raise questions about the clinical relevance of the association, effect sizes may be more substantial when studying relevant subgroups. The importance of finding subgroups is illustrated by the population-based study on cortisol and CFS, in which hypocortisolism was only found in patients with childhood trauma [29].

As it is costly to study stress responsive system function in sufficiently large epidemiological cohorts, another interesting way to promote understanding of dysfunction of stress responsive systems as a causal risk factor of the etiology of FSDs is doing research on treatment studies. Using evidence-based treatments, this strategy may provide information as to whether measures of stress responsive system function predict treatment response or change when the FSD improves. For example, hypocortisolism and a flattened diurnal release of cortisol were associated with a

poorer response to cognitive behavioral therapy in CFS [57], suggesting that patients' neuroendocrine profile may be relevant in choosing the optimal treatment strategy. Ultimately, a risk factor can only be proven to be causal when it has the ability to change the outcome in randomized controlled trials. As a second step, therefore, the benefits of treatments targeting stress-responsive system dysfunction could be studied. Importantly, ignoring strong moderators of treatment response may lead to inclusion of many subjects for whom the interventions are not appropriate, or perhaps are even harmful, and may attenuate effect sizes. In fact, weak effects associated with various treatments for FSDs [54,67] may be due to lack of information on moderators and mediators of treatment. Instead, interventions should be targeted to relevant subgroups [68].

Concluding remarks

In conclusion, although not a *condition sine qua non* for FSDs in general, stress responsive system dysfunction may be involved in the etiology and treatment strategy in subgroups of patients. Such subgroups need to be better identified. As several studies begin to gather multiple waves of stress responsive system data and important covariates over the course of many years, the role of and time scales over which changes contribute to FSDs should be increasingly illuminated. This approach likely represents the best strategy by which we can improve our understanding of this association.

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